



Steroid transnasal nebulization in the treatment of chronic rhinosinusitis

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Purpose of review

Chronic rhinosinusitis (CRS) is a challenging disease entity, affecting 8–15% of the general population. Topical steroids have been recommended as an integral part of the strategy for management of CRS. This review focuses on steroid transnasal nebulization as an alternative treatment option for CRS treatment.

Recent findings

Modern inhalation devices comprise nebulizers, pressurized metered-dose inhalers and dry powder inhalers. Transnasal nebulization with pulsating flow can enhance sinus ventilation and increase drug deposition with longer residence time. Short-term steroid transnasal nebulization provides an effective and safe treatment option for CRS patients, as evidenced by significant clinically relevant improvements and lack of serious side-effects. The underlying mechanisms involve a combination of reduction in inflammatory cells, suppression of inflammatory cell-associated cytokines and chemotactic factors, and regulation of tissue remodeling. Efficacy of transnasal nebulization outweighs commonly used nasal sprays and nasal irrigation as delivery options for topical steroids; however, long-term safety with nebulized steroids needs to be investigated further.

Summary

Steroid transnasal nebulization offers an alternative or a complementary treatment option to nasal sprays and nasal irrigation for management of patients with CRS. Long-term dose-dependent studies with nebulized steroids will be needed to fully appreciate the benefits of this treatment modality.

Keywords

chronic rhinosinusitis, drug deposition, drug residence time, sinus ventilation, steroid transnasal nebulization

INTRODUCTION

Chronic rhinosinusitis (CRS) is a major healthcare problem, which affects 8–15% of the general population, and imposes a significant burden both in terms of expenditure and poor quality of life of affected individuals [1,2]. CRS is a challenging disease entity with a wide diversity of inflammatory subtypes [3]; and given the inflammatory nature of the disease, anti-inflammatory agents such as corticosteroids form principle components of current guidelines for the management of CRS [4]. Although topical intranasal steroid sprays have proved to be an effective treatment and maintain a minimal risk profile [5,6], long-term administration of nasal spray is necessary to obtain persistent effect [7]. Furthermore, despite providing more potent and rapid benefits in controlling inflammation associated with CRS [8,9], systemic corticosteroids have significant side-effects such as hypothalamic-pituitary-adrenal (HPA) axis dysfunction. Therefore, a requirement has arisen for an alternative form of

topical therapy that is more potent than the currently available intranasal corticosteroid sprays, but safer than the systemic steroids in CRS patients.

Administration of steroids by inhalation for treatment of respiratory diseases such as asthma and chronic obstructive pulmonary disease has been shown to be highly efficacious and safe [10–12], particularly because this route of administration

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KEY POINTS

- Pulsating aerosol delivery technique used in transnasal nebulization enhances sinus ventilation and increases drug deposition and residence time in the deeper posterior parts of the nasal cavity, including maxillary, ethmoidal, and sphenoid sinuses.
- Short-term steroid transnasal nebulization provides an effective and well tolerated treatment option for CRS patients, as evidenced by significant improvements in symptom scores, reduction in inflammatory indices, reduction of nasal polyp size, and absence of HPA axis suppression and any serious side-effects.
- Efficacy of steroid transnasal nebulization is superior to intranasal corticosteroid sprays, as evidenced by delivery of higher drug dose, increased area of drug distribution, and prolonged residence time.
- Steroid transnasal nebulization outweighs nasal irrigation based on delivery of a more concentrated dose, droplets of optimal size, and higher systemic availability.
- The mechanisms underlying steroid transnasal nebulization in CRS involve a combination of reduction in inflammatory cells, suppression of related cytokines and chemotactic factors, and regulation of tissue remodeling.

targets the affected sites with high-drug concentrations and bypasses the first-pass metabolism in the liver [13]. Accumulating evidence suggests that aerosol treatment could also deliver drug to upper respiratory airway and facilitate steroid deposition in the sinuses [14,15]. Thus, this article discusses the use of steroids transnasal nebulization as an alternative, and possibly more efficacious, treatment option for patients with CRS.

INHALATION THERAPY HISTORY AND DRUG DELIVERY DEVICES

Inhalation has been employed as a method for delivering medications for thousands of years and the origins of inhaled therapy can be traced back to the ancient Egyptians, South and Central American Indians, Chinese, and Greeks, who inhaled vapors of plants to treat breathlessness and cough [16]. Although the English physician John Mudge first used the word 'inhaler' and advocated inhalation therapy in 1778, the first pressurized inhaler was invented 80 years later by Sales-Girons in France. The British Pharmacopoeia marked formal medical acceptance for inhalation therapy until 1867 and physicians experimented ideas of devices for drug delivery at the beginning of the Industrial

Revolution. The first nebulization device was invented to atomize liquid medicine in the early 1860s and 70 years later, early compressor nebulizers (Pneumostat) were used to deliver adrenal extracts. In 1950, pneumonia was treated with inhaled corticosteroid as anti-inflammatory agent and 20 years later, beclomethasone was marketed as the first inhaled steroid. Subsequently, numerous steroids were developed for inhalation therapy, including budesonide, which was launched in 1987 by Astra Zeneca.

Many of the principles used by the early pioneers are still embodied in modern devices and modern inhalation devices can generally be classified into three categories: nebulizers, pressurized metered-dose inhaler (pMDI), and dry powder inhaler. Nebulizers are the most historical devices for aerosol therapy and comprise two main types: the jet and ultrasonic nebulizers, respectively [16]. A jet nebulizer functions on the basis of Bernoulli's principle, whereby drug solutions are shattered into aerosol droplets by passing compressed gas (air or oxygen) through the solution at high velocity. In contrast, an ultrasonic nebulizer uses high-frequency vibration to produce aerosols; the higher the frequency, the smaller the droplets [17]. Although nebulizers are able to aerosolize most drug solutions and deliver large doses, they have a major drawback in that they are noisy, less portable, time-consuming, and inefficient, with up to 50% drug wastage occurring during continuous operation. The pMDI on the other hand, is a portable outpatient aerosol delivery device, which is widely used currently. However, a major drawback in pMDI use is that it requires proper hand–mouth coordination and the high velocity and large particle size of the aerosol generated can lead to considerable oropharyngeal deposition of the aerosol, resulting in less medication getting into the lungs than intended. In contrast to pMDI, breath-actuated dry powder inhaler requires no hand–mouth coordination, but as the respirable dose delivered depends on the inspiratory flow rate [18], this type of device is not suitable for elderly patients and young children.

SINUS VENTILATION, AEROSOL DEPOSITION, AND DRUG RETENTION IN TRANSNASAL NEBULIZATION

Topical nasal medications administered into the nasal cavity by nasal drops, aqueous spray pumps, and nebulizers have become widely prescribed forms of treatment for sinonasal inflammatory diseases, such as CRS and allergic rhinitis. However, despite their wide usage, the success of topical drug delivery into the nose and particularly the paranasal

sinuses in CRS patients remains a challenge, partly because the sinus cavities are usually poorly ventilated in CRS and most nasally administered drugs fail to reach the sinuses [19].

The sinuses are normally hollow, nonactively ventilated organs with a capacity of 5–30 ml, and thus for efficient drug delivery into the sinuses paranasal sinus ventilation is a primary requirement. While diffusion and pressure-induced flow contribute to aerosol transport into sinuses, pulsating aerosol delivery offers an alternative option to actively enhance sinus ventilation. Pulsating airflows are used to generate pressure gradients and have been shown to enhance ventilation efficiency and drug deposition in the paranasal sinus [15,20–22]. However, efficient delivery of the aerosol into the sinus cavities is dependent on the aerosol droplets being below 5 μm mass median aerodynamic diameter in size, as larger particles tend to deposit in the nasal cavity by inertial impaction. Moreover, although pulsating aerosols can access and deposit the drug in the deeper posterior parts of the nasal cavity, including maxillary, ethmoidal, and sphenoid sinuses, these cannot deliver detectable amounts of the drug into the frontal sinus [23²⁴]. While drug penetration into the lung and unwanted side-effects could be avoided by closure of the soft palate during aerosol delivery, this technique requires proper instruction and training to achieve optimal effect and improve patient compliance.

Although aqueous spray pump is the most commonly used method for delivery of intranasal drugs, transnasal nebulization appears to be a more effective method [14,24–26]. Particle deposition analyzed using a computational fluid dynamics model of the human nose has demonstrated that a nasal nebulizer increased aerosol particle deposition beyond the anterior nasal cavity and covered greater surface area compared with nasal sprays [24]. It is possible that this might be because of the fact that larger particles created by nasal sprays are likely to deposit directly in the nasal vault while smaller particles created by a nebulizer are more likely to reach the sinus [27]. Furthermore, a nasal nebulizer releases smaller slow moving aerosol particles (<10 μm) to minimize the inertial impaction in the anterior nasal cavity than spray pumps, which release larger rapidly moving aerosol particles (>20 μm) [24]. However, it has been reported that nasal deposition of aerosol particles is highest with an optimal particle diameter greater than 6.42 μm during nebulization in the presence of nasal septal deviation, whereas particles with smaller size (nearly 100% of particles <6.42 μm) might bypass the nasal cavity altogether without deposition [24]. In contrast, several studies have demonstrated that while

nasal pump sprays deliver the vast majority of the drug in the nasal cavity, without significant amounts being detectable in either the sinus cavities or the lung [28], pulsating aerosol delivery deposits between 4 and 8% of the drug into the sinuses [14,19,21]. Moreover, the delivery by pulsation appears to be associated with a delayed clearance and three-fold longer residence time of the drug at the site of deposition compared with nasal pump sprays, thus allowing the frequency of drug administration to be reduced [14].

EFFICACY AND SAFETY OF STEROID ADMINISTERED BY TRANSNASAL NEBULIZATION

Topical corticosteroids have been recommended as an integral part of the strategy for the management of CRS [4]. Clinically, corticosteroids are widely available as nasal irrigation solutions or delivered as aqueous sprays from hand-held pumps for topical treatment of sinonasal inflammatory diseases. More recently, a new option for topical corticosteroids treatment in the CRS has been the off-label use of steroid inhalation suspension, by transnasal nebulization. A randomized, double-blind, placebo-controlled study by Wang and colleagues [29³⁰] has recently indicated that twice daily administration of budesonide inhalation suspension via a pulsating atomization device (i.e. budesonide transnasal nebulization) was an effective treatment in patients with eosinophilic CRS with nasal polyps, as evidenced by significant improvements in symptom scores, reduction of nasal polyp size, and improvements in several inflammatory markers. Similarly, while one study [30] has shown topical nebulized budesonide to be effective in reducing the need for systemic prednisone and improved global assessment scores in refractory postoperative CRS patients, another recent study [31³²] has shown that nebulized budesonide was significantly more effective than budesonide administered by nasal spray, and equally effective as oral prednisolone, in improving olfactory function in CRS patients.

The efficacy of topical steroids may generally be affected by the dose delivered to the study participant and the site of deposition in the airway [13]. As a first step of topical therapy, although the amount of drug deposited in the nasal mucosa is greater with nasal sprays, nebulization increases the volume of delivery with relatively higher quantities of steroids compared with nasal spray [14,19,21,32–34] (Table 1). Indeed, it has been estimated that a 1-min pulsating aerosol delivery can deposit comparable amounts to two puffs of a nasal pump spray in the nasal cavity and 10–15 μl of the nebulized

Table 1. Daily administered dose of budesonide via nasal nebulization and nasal spray

	Nasal nebulization	Nasal spray
Product	Pulmicort Respules	Rhinocort
Daily-labeled dose	2 mg	512 µg
Nasal deposition	500–1420 µg (25% [21]–71% [14] of labeled dose)	512 µg (100% of labeled dose [19,32])
Systemic availability	260–300 µg (13–15% of labeled dose, inhaled orally [33])	174 µg (34% of labeled dose [34])

solution into the sinus [23[■]]. Furthermore, as topical steroids can be absorbed into the systemic circulation through the airway, the availability of the steroid in the nose is also influenced by the highly vascular nature of the nasal mucosa, which facilitates direct topical absorption. In this regard, evidence suggests that the amount of drug lost through systemic absorption in the nose is markedly low when delivered by nebulization then when delivered by nasal spray [33,34] (Table 1). Collectively, these studies suggest that transnasal nebulization may provide a sufficient amount of drug for topical therapy.

Apart from the advantage of dose, accumulating evidence from both in-vitro [15] and in-vivo [14,28,31[■]] studies supports the view that nebulization distributes the drug over a greater area and with increased residence time in the sinuses than nasal sprays. Indeed, Reychler and colleagues [31[■]] have suggested that the significantly greater improvement in olfactory function noted with budesonide transnasal nebulization, compared with the effect of budesonide delivered with nasal spray, was a consequence of the modalities of the delivery, rather than significant differences in the amounts of drug delivered onto the olfactory epithelium. Moreover, the finding that reductions in polyp size after 2-week budesonide transnasal nebulization [29[■]] are comparable with that obtained after 4 weeks' treatment with budesonide nasal spray [35] suggests that steroid treatment by transnasal nebulization may possibly confer a faster onset of action in CRS patients.

Neither nasal irrigation nor transnasal nebulization is the on-label modality of budesonide inhalation suspension, but both drug delivery methods have been employed in clinical practice. The efficacy of budesonide inhalation suspension as a nasal lavage or irrigation in patients with CRS has been investigated in several studies [36–38]. One recent study [39[■]] has compared the efficacy and safety of nebulized budesonide 1 mg twice daily for 2 months with budesonide impregnated nasal saline irrigation in CRS patients, and demonstrated that nebulized budesonide significantly improved the SNOT-22 scores compared with budesonide nasal irrigation.

Nebulization delivered a more concentrated dose of aqueous budesonide than nasal irrigation, and produced droplets of optimal size for deposition across a broad surface area of nasal mucosa. Other studies have shown that while a nebulizer-compressor system produced systemic availability of 13% of labeled dose in healthy adults [33], nasal irrigation led to delivery of less than 5% of the total drug in sinuses of most patients [38].

Safety of corticosteroids is a matter of great clinical importance because topical steroids at high doses have been shown to be associated with potential systemic side-effects, such as suppression of HPA axis and reduction of endogenous cortisol levels. In this respect, Thamboo and colleagues [39[■]] have suggested that use of nebulized budesonide (1 mg twice daily for 60 days) is a well tolerated treatment option for CRS patients, as the authors were unable to detect any adrenal suppression in these patients. In accordance with these findings, we have also demonstrated that transnasal nebulized budesonide (1 mg twice daily for 2 weeks) is a clinically well tolerated treatment option in eosinophilic CRS patients, as it neither suppressed HPA axis, significantly reduced morning plasma cortisol levels, nor produced any clinically relevant adverse effects after [29[■]]. However, as the dose of budesonide used in these studies was twice as high as has been advocated for maintenance treatment, long-term dose-dependent studies with nebulized budesonide will be needed to fully appreciate the benefits of this treatment modality for management of CRS or other chronic inflammatory nasal condition.

MECHANISMS UNDERLYING STEROID TRANSNASAL NEBULIZATION

Given the inflammatory nature of CRS, treatment of the underlying inflammation, apart from controlling the symptoms, is central to successful management of the condition. The anti-inflammatory mechanisms underlying corticosteroid therapy generally involve a combination of reduction in inflammatory cells, suppression of inflammatory cell-associated cytokines and chemotactic factors, and regulation of tissue remodeling.

A study [29^{***}] of patients with eosinophilic CRS, has demonstrated that treatment for 2 weeks with budesonide transnasal nebulization (1 mg twice, daily) significantly inhibited eosinophil infiltration, accompanied by lower eotaxin production. Concomitantly, Th2-biased inflammation was also significantly attenuated as evidenced by reduction of Th2 cell numbers and decrease of IL-5 levels in nasal polyps. These are consistent with those of Van Zele and colleagues [9], who showed that oral steroids significantly reduced the levels of ECP and IL-5 in nasal secretions of patients with CRSwNP [9]. In contrast, Th1/Th17-mixed inflammation, which has commonly been associated with neutrophil abundance, has been shown to exhibit reduced sensitivity to corticosteroids [29^{***},40]. Indeed, treatment with budesonide transnasal nebulization was not found to significantly alter the levels of cytokines IFN- γ and IL-17 compared with placebo nebulization, but was found to significantly increase the frequencies of natural regulatory T (nTreg) cells and Tr1 cells [29^{***}]. The finding for elevated levels of regulatory T cells with budesonide transnasal nebulization has also been demonstrated for treatment of patients with CRSwNP, with intranasal mometasone [41].

Another important cytokine, transforming growth factor beta (TGF- β), has also been shown to be increased after topical corticosteroids treatment, and was associated with elevation of regulatory T cells and suppression of ongoing inflammatory responses [29^{***},42]. Additionally, TGF- β was likely to play a critical role in airway remodeling through the induction of different profibrotic processes [43]. In this respect, excessive collagen deposition in nasal polyp after budesonide transnasal nebulization has been shown to coincide with a significant increase in TGF- β , as well as a significant decrease in matrix metalloproteinases (MMPs) and significant in tissue inhibitors of metalloproteinases (TIMPs) [29^{***},44]. This finding may be of particular relevance because the balance between MMPs and TIMPs is important for homeostasis of collagen synthesis and breakdown, and lower expression of MMPs and higher amount of TIMPs are likely to be regulated by increased TGF- β expression [45]. It is possible that budesonide treatment downregulates the expression of MMPs at their main cell source level, although this needs to be confirmed in future studies.

CONCLUSION

Budesonide transnasal nebulization targets the site of inflammation, and allows drug deposition with longer residence time. This new topical treatment in CRS may achieve significant clinical improvements

by regulating cytokine expression, T-cell subsets, and tissue remodeling, in the absence of any serious side-effects. Budesonide transnasal nebulization could be investigated as an alternative or a complementary treatment option for the control of CRS, although long-term dose-dependent studies with nebulized budesonide would be required to fully appreciate the benefits of this treatment modality.

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Conflicts of interest

There are no conflicts of interest.

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